Novel treatments for Depression: ECT, brain implants and magic mushrooms

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Objectives

- 1 Identify newer treatment could recently added to the marketplace that could be novel treatments for depression
- 2. Describe the use of quick acting nasal ketamine and its potential side effects
- 3. Identify selective NMDA antagonists, partial NMDA agonists, glutamate inhibitors and their role in reversing depressive symptoms
- 4. Describe the use of brain stimulators and magnetic seizure therapy
- 5. Describe psylocybin mechanism of action and effects
- 6. Identify what advances in therapy may be on the horizon

MDD

Lifetime prevalence in US 16.9% (pre-Covid)

Suicidal risk

Functional impairment (9th leading cause)

Years lost to disability (leading cause)

Antidepressants

- Outcome suboptimal: side effects, slow response, inadequate treatment efficacy
- First line antidepressant effectiveness: 30%
- 4 step treatment: 67%
- Augmentation with atypical antipsychotic: 44.2%
- Affects 320 billion people worldwide, 16 million in US/yr

Modulating the Glutamatergic System

- NMDA receptor: memory, anxiety and depression
  - 1. Ketamine and other Nonselective NMDA Receptor Antagonists
  - 2. Selective NMDA Receptor Subtype 2B (NR2B) Antagonists
  - NMDA partial Agonists
  - Glutamate Release Inhibitors
  - Metabotropic Glutamate Receptor Antagonist

Ketamine

IV: Short term effect occurs in 4 hours, lasts 3-7 days

- May be used for those resistant to ECT and stops suicidal ideation

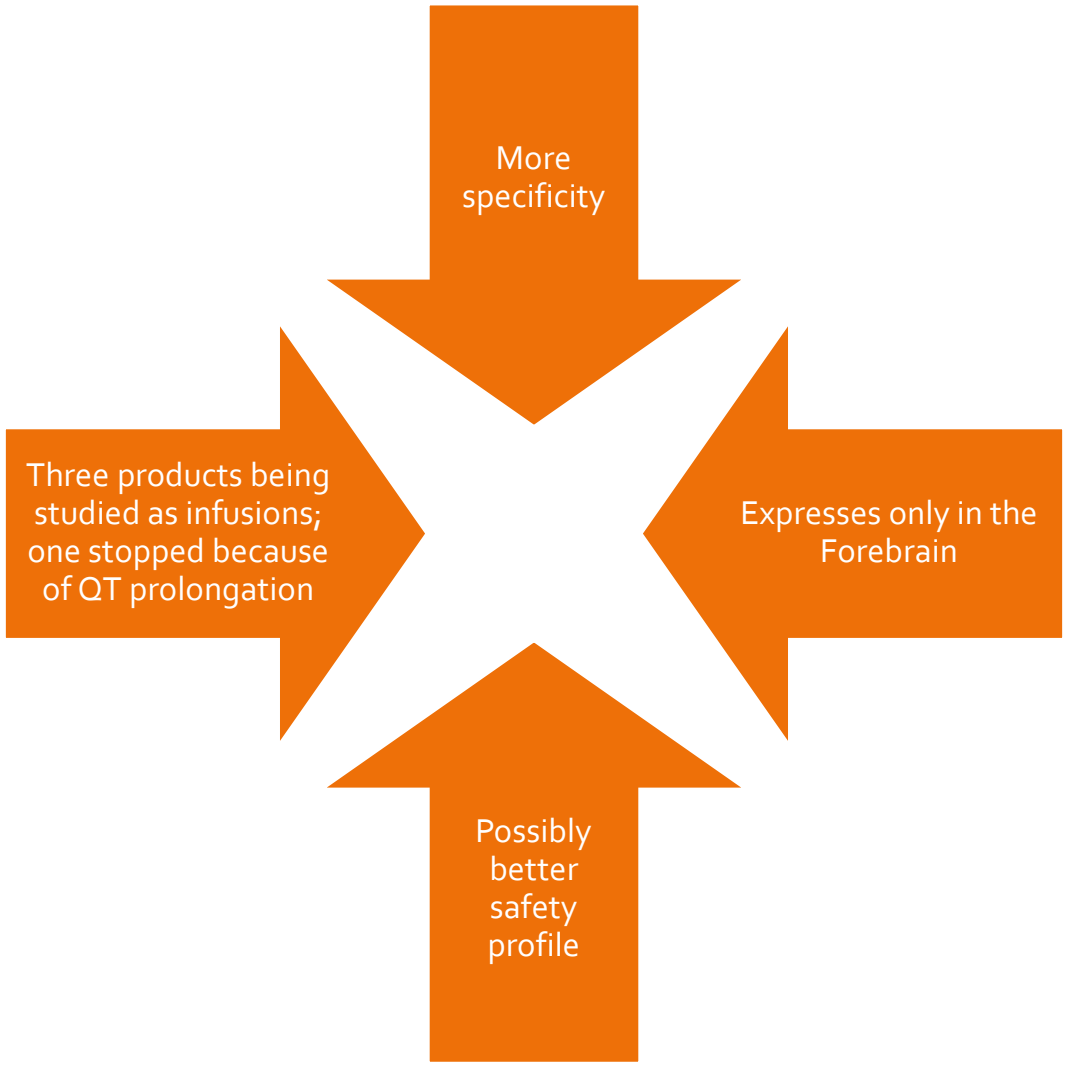
Intranasal ketamine improves depressive symptoms in 24 hours

Long term effect: 27% maintained antidepressant effect for28 days following single dose; 71% after IV dose 6 times in 12 days

Median time to relapse 18 days

Very complicated MOA involving AMPA receptor activities and NMDA receptor suppression

Side effects: psychotomimetic effects, cognitive impairment, abuse and dependance



Selective NMDA Receptor Subtype 2 B Antagonists

NMDA Partial Agonist

NMDA receptor modulators

- Agonist effect at low doses
- Antagonists at high doses

Three products being studied:

- D-cycloserine
- GLYX-13
- Seocosine

Glutamate Release Inhibitors

- Riluzole
  - Inhibits glutamate release
  - Increases glutamate reuptake
  - Blocks NMDA receptor activity
  - Increases AMPA receptor trafficking
  - May restore hippocampal expression and improve depressive symptoms

Metabotropic Glutamate Receptor Antagonist

- Coadministration of low doses can enhance the antidepressant effects of scopolamine and ketamine
- Clinician rated scales showed little improvement, but patient rated scales showed significant improvement

Brain Stimulation

Depressive disorders:

- Impaired neurocirculatory activity
- Reduced neuroplasticity (brain's ability to change)

ECT

Transcranial Magnetic Stimulation (TMS)

Transcranial direct current stimulation

Cranial electrotherapy stimulation

Magnetic seizure therapy

Useful in treating depression refractory to medications

One of the oldest brain stimulator therapies

Increases hippocampal connectivity and volume

Stimulates neurogenesis in the frontal brain

Modulates white matter microstructure in pathways connecting frontal and limbic systems

Decreases glutamate content

Synergistic effect with ketamine

ECT

Less cognitive side effects than ECT

Uses an electromagnetic coil on the scalp to create an alternating magnetic field, which induces a secondary electric current in the brain without interference from the skin muscle or bone

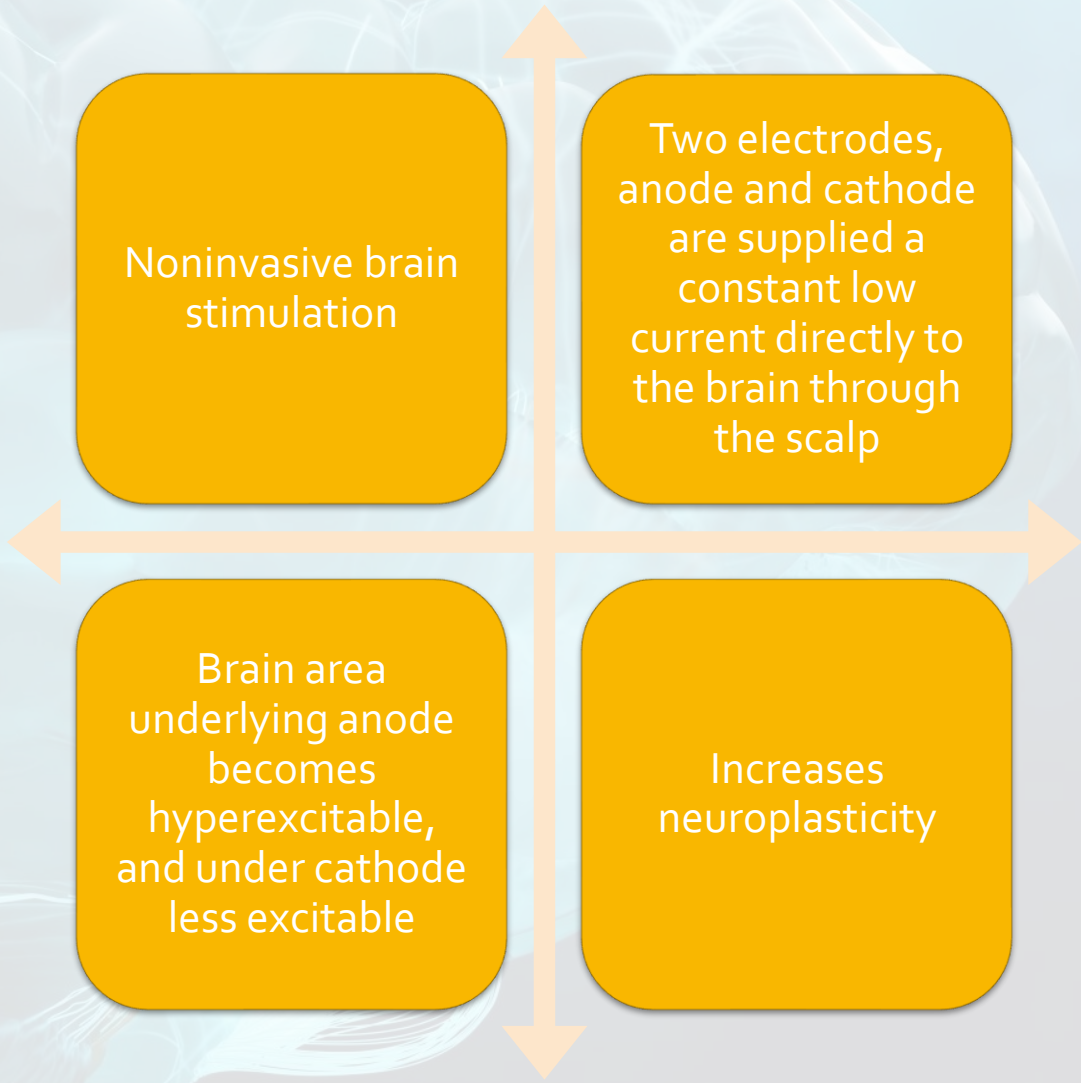
Stimulates neurogenesis

Modulates brain activity and neurotransmitters such as serotonin and dopamine

Not used currently as monotherapy

Transcranial Magnetic Stimulation

Transcranial Direct Current Stimulation



Cranial electrotherapy stimulation

- Pulsed low amplitude eclectic currents to the brain via scalp electrodes
- Approved for the treatment of anxiety, depression, and insomnia
- May be used for comorbid depression in anxiety
- May deactivate cortical brain activity and alter connectivity

Magnetic Seizure Therapy

A variant of TMS , based on ECT using high intensity stimulation to evoke seizures like with ECT but with better control

Response rate of 50-60%

Psilocybin therapy

- May be the biggest advance in mental health sine the use of Prozac in the 1990s
- In a study published last year in JAMA Psychiatry, the therapy was 4 times mor effective than traditional antidepressants. Two thirds of participants:
  - 50% reduction in symptoms after 1 week
  - After 4 week, >50% were in remission, and didn't qualify as being depressed

Larger clinical trials in US and Europe ; 300 patients in 10 countries; given "breakthrough therapy" status by US FDA in 2018 1nd 2019.

Protocols that combine psilocybin and psychotherapy and treatments slated for 2024

Psilocybin history

Indigenous populations used for millennia

1943 a chemist, Albert Hoffman injested accidentally LSD, causing him to enter a dreamlike state with hallucinations.

He was convinced it was useful in medicine and psychiatry

Manhattan banker, R Gordon Wasson took a trip to Oaxaca, Mexico, sampled these mushrooms and published 15 page account of his psychedelic experience

1960s: more than 700 alcoholics were dosed by psychiatrists more than half stayed sober for several months. Others used them for anxiety, depression, angst of terminal cancer patients and other mental health disorders

Counter culture embraced them for recreation: suicides, bad trips mental breakdowns led to federal research money drying up

MOA

Serotonin receptor activity, that lingers for hours, not washing out as normal receptor neurotransmitters do. This prompted FDA relook. MOA theorized to be MOA inhibition, blocking breakdown of brain chemicals

1990s: FDA open to applications to study psychedelic drugs

2000's : clinical trials on terminally ill cancer patients and adiiction patients

Psilocybin profoundly disrupts the normal communication pattern in the brain. They interfere with the connectivity and functioning of brain structures involved in executive planning.

- Additionally interferes with functioning of thalamic reticular nucleus: volume control in incoming messages
- Shut down "default mode network" involved in daydreaming; hyperactive in depressed and anxious individuals self talk/ rumination

MOA

Narrowed mental and behavioral repertoire

Aberrant brain activity and circuits get "stuck" in rigid communication patterns

Brain loses the ability to be flexible and nimbleness that allows it to respond favorable to new situations and environments

Reset: drug wears off and leads to a reset of brain patterns…..how?

MOA

- Do the drugs prompt the brain to release growth agents allowing the brain cells to rewire themselves and forge new connections?
- Do these drugs catalyze the brain to begin regenerating itself?
- Chronic stress and depression reduce these neuronal connections and cause existing one to shrivel. After psilocybin ingestion, the dendrites bloomed, even after a single dose even a month later (***Fantastic Fungi on Netflix)
- Micro-dosing is a popular practice in those that want to experience the product
- Neurogenesis: drugs wedge serotonin receptors to the on position for a longer period of time

MOA and chemistry

The effects of psilocybin mushrooms come from psilocybin and psilocin. When psilocybin is ingested, it is broken down by the liver in a process called dephosphorylation. The resulting compound is called psilocin, which is responsible for the psychedelic effects.

Psilocybin and psilocin create short-term increases in tolerance of users, thus making it difficult to misuse them because the more often they are taken within a short period of time, the weaker the resultant effects are.

Psilocybin mushrooms have not been known to cause physical or psychological dependence (addiction)

The psychedelic effects tend to appear around 20 minutes after ingestion and can last up to 6 hours. Physical effects including nausea, vomiting, euphoria, muscle weakness or relaxation, drowsiness, and lack of coordination may occur

Effects

As with many psychedelic substances, the effects of psychedelic mushrooms are subjective and can vary considerably among individual users.

The mind-altering effects of psilocybin-containing mushrooms typically last from three to eight hours depending on dosage, preparation method, and personal metabolism.

The first 3–4 hours after ingestion are typically referred to as the 'peak'—in which the user experiences more vivid visuals and distortions in reality.

The effects can seem to last much longer to the user because of psilocybin's ability to alter time perception

Sensory Effects

Sensory effects include visual and auditory hallucinations followed by emotional changes and altered perception of time and space.

Noticeable changes to the auditory, visual, and tactile senses may become apparent around 30 minutes to an hour after ingestion, although effects may take up to two hours to take place.

These shifts in perception visually include enhancement and contrasting of colors, strange light phenomena (such as auras or "halos" around light sources), increased visual acuity, surfaces that seem to ripple, shimmer, or breathe; objects that warp, morph, or change solid colors; a sense of melting into trails behind moving objects

Sounds may seem to have increased clarity—music, for example, can take on a profound sense of cadence and depth. Some users experience synesthesia, wherein they perceive, for example, a visualization of color upon hearing a particular sound.

Emotional Reactions

The psychological consequences of psilocybin use include hallucinations and an inability to discern fantasy from reality.

Panic reactions and psychosis also may occur, particularly if a user ingests a large dose.

In addition to the risks associated with ingestion of psilocybin, individuals who seek to use psilocybin mushrooms also risk poisoning if one of the many varieties of poisonous mushrooms is confused with a psilocybin mushroom.

What's ahead?

- FDA approval:
  - Special provisions stipulating the drugs can not taken outside the clinical setting
  - Must be carefully controlled
  - May only be administered by a trained healthcare provider

  - Psilocybin services to be legalized in Washington State Jan 6, 2022
    - Adults 21 and older
    - Go to licensed service center
    - Specialized diagnosis
    - Seattle becomes the largest US city to decriminalize psychedelics
    - Would be legal regulated industry

Questions?